IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Juan Colberg, et al.	**Examiner:**	Mark L. Berch
Serial No.:	10/781,158	**Art Unit:**	1624
Filed:	February 17, 2004	**Docket No.**	PC10856B

For: PROCESS AND ESTER DERIVATIVES USEFUL FOR PREPARATION OF CEPHALOSPORINS

Confirmation No.:
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22314-1450

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

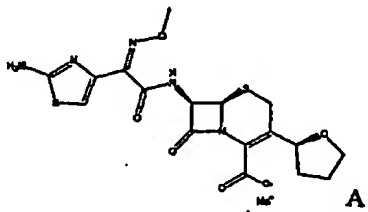
I, JUAN C. COLBERG, declare and state as follows:

1. I received a PhD degree in organic Chemistry from University of Puerto Rico, Rio Piedras Campus, San Juan Puerto Rico, in 1994. Attached as Exhibit A is a copy of my Curriculum Vitae which indicates some of the reports and papers I have published, the awards I have won, and my employment history;

2. from 1993 to present I have been and continue to be employed at Pfizer Inc., the assignee of the above-identified application;

3. I am a co-inventor in the above-referenced patent application;

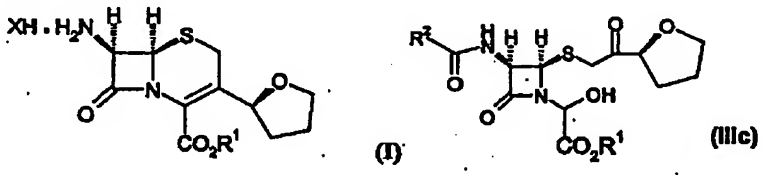
4. I was a member of a team which investigated the development of a commercial process for the synthesis of a long-acting cephalosporin of formula A, which is known under the generic name cefovecin, and which is described in US Patent No. 6,001,997;



A

5. my group, in developing a commercial process for producing cefovecin and its intermediates, studied the process of Bateson, set forth in US Patent No. 6,001,997;

6. the processes set forth in Bateson for the preparation of intermediates of cefovecin of formulae I and IIIc



(I) (IIIc)

where CO_2R^1 is an ester derivative, $R^2C(O)$ is an acyl group and X is halo, were deemed inadequate for commercialisation compared to the processes my group developed, as established by the claims of the above-identified application;

7. to substantiate the superiority of the processes defined by the claims of the present application, the processes disclosed by Bateson were compared to the claimed processes of the above-identified application in experiments conducted by me or under my supervision;

8. for the synthesis of a compound of formula I, utilizing the Bateson process, an ester compound of formula IIIc, where R^1 is *para*-methoxybenzyl and R^2 is phenyl, was converted to a compound of formula I, where R^1 is *para*-methoxybenzyl and X is chloro, using the four step process set out in Example 1 of the above-identified application;

9. the form and purity of the resulting compound of formula I from the reaction was unacceptable for further use due to an unacceptable high level of impurities. The crude product required purification by column chromatography and the compound of formula I was obtained in an overall yield of 22% as a yellow foam. The yield was defined as the mass of the compound of formula I obtained as a percentage of the theoretical yield of the compound of formula I for the four step process;

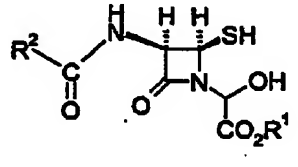
10. the Bateson process was compared with the process of present claim 1 wherein the compound of formula IIIc, where R^1 is *para*-nitrobenzyl and R^2 is

phenyl, to produce a compound of formula I, where R^1 is *para*-nitrobenzyl and X is chloro;

11. the compound of formula I obtained by the practice of the process of claim 1 of the present application was in a crystalline solid form of sufficiently high purity so that no purification operations were necessary prior to further use. The compound of formula I was obtained in a yield of 45%, where yield is again defined as the mass of the compound of formula I obtained as a percentage of the theoretical yield of the compound of formula I for the four step process;

12. the above results establish the clear superiority of the present process of claim 1 over the Bateson process. That the compound having the formula I was produced and isolated in acceptable purity and with higher yields, as set forth in Example 1 of the specification of the present application, and that it was very useful in the synthesis of cefovecin, was surprising;

13. for synthesis of a compound of formula IIIc, further utilising the Bateson process, an ester compound of formula V



(V)

where R^1 is *para*-methoxybenzyl and R^2 is phenyl, was converted to a compound of formula IIIc, by treatment with 2-bromo-1-(tetrahydro-furan-2-yl)-ethanone, under the process set out in Example 5 of the above-identified application, where the compound of formula V is generated *in situ*;

14. the form and purity of the compound of formula IIIc resulting from the reaction was unacceptable for further use due to an unacceptable high level of impurities. The crude product required purification by column chromatography and the compound of formula I was obtained in an overall yield of 55% as a white foam, where the yield is again defined as the mass of the compound of formula IIIc obtained as a percentage of the theoretical yield of the compound of formula IIIc for the process;

15. the Bateson process for preparation of a compound of formula IIIc was compared with the process of claim 10 in the present application for the compound of formula V, where R^1 is *para*-nitrobenzyl and R^2 is phenyl, to produce a compound of formula IIIc, where R^1 is *para*-nitrobenzyl and R^2 is phenyl;

16. the compound of formula IIIc obtained by the practice of the process of claim 10 was in a solid form of sufficiently high purity so that no purification operations were necessary prior to further use. The compound of formula IIIc was obtained in a yield of 86%, where yield is again defined as the mass of the compound of formula IIIc obtained as a percentage of the theoretical yield of the compound of formula IIIc for the process;

17. the above results establish the clear superiority of the present process of claim 10 over the Bateson process. That the compound having the formula IIIc was produced and isolated in acceptable form and with higher yields, as set forth in Example 5 of the specification of the present application, and that it was very useful in the synthesis of cefovecin, was surprising; and

18. that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine, imprisonment, or both, under section 1001 of title 18 of the United States code and such wilful false statements may jeopardize the validity of the application or any patent issuing thereon;

Further declarant sayeth not.

JUNE 17, 2006

Date

Juan C. Colberg

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SECOND DECLARATION UNDER 37 C.F.R. §1.132

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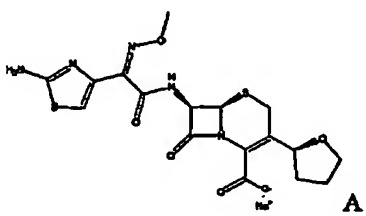

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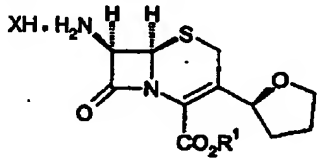
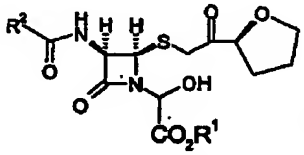


(I)



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where CO_2R^1 is an ester derivative, $R^2C(O)$ is an acyl group and X is halo, were deemed inadequate for commercialisation compared to the processes my group developed, as established by the claims of the above-identified application;

7. to substantiate the superiority of the processes defined by the claims of the present application, the processes disclosed by Bateson were compared to the claimed processes of the above-identified application in experiments conducted by me or under my supervision;

8. for the synthesis of a compound of formula I, utilizing the Bateson process, an ester compound of formula IIIc, where R^1 is *para*-methoxybenzyl and R^2 is phenyl, was converted to a compound of formula I, where R^1 is *para*-methoxybenzyl and X is chloro, using the four step process set out in Example 1 of the above-identified application;

9. the Bateson process was compared with the process of present claim 1 wherein the compound of formula IIIc, where R^1 is *para*-nitrobenzyl and R^2 is phenyl, to produce a compound of formula I, where R^1 is *para*-nitrobenzyl and X is chloro;

10. removal of either the *para*-methoxybenzyl (Bateson's process) or the *para*-nitrobenzyl (Applicant's process) protecting group under acidic conditions resulted in similar yields of 20-40%, where yield is defined as the mass of the compound of formula I obtained as a percentage of the theoretical yield of the compound of formula I for the four step process;

11. removal of either the *para*-methoxybenzyl (Bateson's process) or the *para*-nitrobenzyl (Applicant's process) protecting group using hydrogenation resulted in similar yields of 70-80%, where yield is defined as the mass of the compound of formula I obtained as a percentage of the theoretical yield of the compound of formula I for the four step process;

12. removal of the *para*-nitrobenzyl (Applicant's process) protecting group using sodium dithionite under very mild conditions without the use of hydrogenation conditions, which is not feasible for the *para*-methoxybenzyl (Bateson's process) protecting group, resulted in yields of 85-90%, where yield is again defined as the mass of the compound of formula I obtained as a percentage of the theoretical yield of the compound of formula I for the four step process;

13. removal of the *para*-nitrobenzyl (Applicant's process) protecting group using sodium dithionite under very mild conditions did not entail the use of palladium;

14. the above results establish the clear superiority of the present process of claim 1 over the Bateson process.

15. The compound having formula I was produced and isolated in acceptable purity and with higher yields, as set forth in Example 1 of the specification of the present application, and it was very useful in the synthesis of cefovecin, and

16. that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine, imprisonment, or both, under section 1001 of title 18 of the United States code and such wilful false statements may jeopardize the validity of the application or any patent issuing thereon;

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